IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant(s):	Weiping Shao	
Serial No:	09/931,736	Art Unit: 1641
Filed:	17 August 2001	Examiner: Deborah A. Davis
Title:	SUPPRESSION OF CROSS-REACTIVITY AND NON-SPECIFIC BINDING BY ANTIBODIES USING PROTEIN A	
Docket No:	469290-76	

27 August 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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APPEAL BRIEF

Sir:

Applicants filed a Notice of Appeal in the above-entitled application on 27 February 2004 wherein Applicants appealed from a final rejection dated 3 December 2003 of claims 1-18 of the above-referenced application for patent. This brief is submitted in triplicate. The claims under appeal are claims 1-4 and 8-18, a copy of which appear in the appendix attached hereto. No request for oral argument is being made. A check in the amount of $1810.00 ($330.00 for this brief plus $1480.00 for a 4 month extension of time to file the brief) is enclosed.

THE REAL PARTY IN INTEREST

Molecular Staging, Inc., of New Haven, CT, is the assignee of this application and is therefor the real party in interest.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF THE CLAIMS

Claims 1-4 and 8-18, the claims under appeal, are active and are all rejected. Claims 3-7 and 19-75 have been canceled.

STATUS OF AMENDMENTS

The amendment under 37 C.F.R. 1.116, filed 27 February 2004, was entered in the Advisory Action, dated 4 May 2004.

SUMMARY OF THE INVENTION

The invention relates to a blocked immunoglobulin comprising an antibody portion and a Protein A portion wherein said antibody portion comprises a member selected from the group consisting of two antibody light chain variable regions, two antibody heavy chain variable regions and a combination thereof. This structure may or

may not be attached to a support. By having a blocked Fc portion the immunoglobulin can be used without the need to avoid unwanted reactions with the Fc site and thereby avoids the need for using fragments of antibodies (as disclosed in the application at page 7, lines 23-28, and at page 9, line 29, over to page 10, line 9).

With the advent of methods of molecular biology and recombinant technology, it is now possible to produce antibody molecules by recombinant means and thereby generate gene sequences that code for specific amino acid sequences found in the polypeptide structure of the antibodies. Regardless of the source of the antibodies, or how they are constructed, all antibodies have a similar overall 3 dimensional structure, often designated H_2L_2 since antibodies commonly comprise 2 light (L) amino acid chains and 2 heavy (H) amino acid chains. Both heavy and chains have "variable" or "V" regions that bind structurally complementary antigenic targets and are characterized by differences in amino acid sequence from antibodies of different antigenic specificity. Each heavy and light chain also possesses a constant region, with the heavy chain constant region being much longer than the variable chain constant region (as supported in the application at page 7, line 30, over to page 9, line 27).

The heavy chain constant regions also possess an Fc region that is antigenic and often responsible for immunogenic reactions when antibodies of one species are introduced into a mammal of a different species. To avoid such cross-reactivity, fragments of antibodies having much of the heavy chains removed are often used. The blocked immunoglobulin of the invention (with the Fc region blocked by Protein A or a fragment of protein A) provides a major advantage in that it obviates the need to form such active fragments in order to avoid the unwanted side reactions produced by the presence of an Fc region.

ISSUES

1. Whether claims 1-4 and 8-18 are unpatentable under 35 U.S.C. 103 over Dorval et al. in view of Cabilly et al.

2. Whether claims 1 and 8-10 are unpatentable under 35 U.S.C. 103 over Sano et al. in view of Cabilly et al.

GROUPING OF THE CLAIMS

Different groups of claims were finally rejected for obviousness based on separate pairs of references. Because both groups 1-4, 8-18 and 1, 8-10 include claim 1 and all remaining claims depend from claim 1, Applicant believes that this Appeal should be considered with regard to claim 1 and therefor no separate groupings are being offered.

ARGUMENT

1. Claims 1-4 and 8-18 were rejected under 35 U.S.C. 103(a) as unpatentable over Dorval et al (U.S. Pat. No. 5,561,045) in view of Cabilly et al (U.S. Pat. No. 4,816,567). The Examiner contends that it would have been obvious to one of ordinary skill in the art to modify the teaching of Dorval et al to include altered immunoglobulins of Cabilly et al that contain heavy and light chain variable regions.

A finding of obviousness requires three conditions:

1. The cited references, in light of the then available general knowledge, must suggest the combination of the references to produce the claimed invention [see: *In re*

Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988)].

2. Combination or modification of the references must have a reasonable expectation of success. [See: *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991)]

3. Combination of the cited references must teach or suggest all of the limitations of the claim(s) [See: *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970)]

Dorval teaches use of an antibody that has a blocked Fc portion to prevent Protein A binding (see Dorval at column 5, line 64, over to column 6, line 7) since Protein A binds the Fc region. Conversely, the claims on appeal recite a blocked immunoglobulin that has a Protein A portion, not one that is blocked to prevent Protein A binding.

Cabilly et al teach the production of chimeric antibodies in which an antigen binding region of an antibody from one species of mammal (such as a mouse) has been coupled with the Fc containing heavy chain region of an antibody of a different species (such as a human). When such an antibody is administered to an animal having the same kind of heavy chain constant region, unwanted reactions at the Fc site are avoided. (See Cabilly et al at column 5, lines 30-35, at column 6, line 65, over to column 7, line 18, at column 30, claim 1 and in the Abstract). In sum, Cabilly is concerned with preparing chimeric and other synthetic antibodies that avoid unwanted side reactions. There is no motivation to use such an antibody in the *in vitro* method of Dorval et al because in Dorval the antibodies have their Fc sites blocked so that unwanted reactions cannot occur – regardless of what kind of antibody is used.

Consequently, no one in the art would be motivated to use a Cabilly chimeric antibody in the analytical procedure of Dorval because each solves the problem of a reactive Fc region in different ways: Dorval by blocking it for *in vitro* analyte detection and Cabilly by using a heavy chain of the same species as the recipient animal, i.e., use of a

Cabilly chimeric antibody obviates any need to block the Fc region. Thus, there is no showing of any motivation to combine these references. Nor would there be because the Cabilly antibodies are exotic chimeric antibodies for use in *in vivo* administration to animals so there is no reason to use them in the *in vitro* analyte measurements of Dorval et al where the Fc region would be chemically blocked and there is no need to form any chimeric antibody to prevent binding to the Fc site.

The Examiner points out that because Applicant's invention claims a product, what this product is used for will not be given patentable weight. Applicant contends that this is certainly true for novelty issues but here the rejection is based on obviousness so that there is an admission that the product is not *per se* disclosed in the art and the use may be relevant if it goes to the motivation to combine. Thus, if the teaching of one reference is useless in the other, or when combination results in a disadvantage, then there is no motivation to combine regardless of whether such combination is technically achievable.

The issue is not whether two references can be combined for some reason but whether there is any motive to combine them for any reason. The Examiner cites In re Dillon, 16 U.S.P.Q.2d 1897, 1904 (Fed. Cir. 1990) for the proposition that the prior art need only suggest a reason to make the claimed invention even if the reason or motivation is different from that of the Applicant. In view of the foregoing, Applicant contends that there is not.

The Examiner further contends that Cabilly et al was relied on for its teaching of the number of light and heavy variable regions in antibodies, how they can be altered and its advantages (see Advisory Action at page 3, bottom 3 lines). Applicant responds that any immunology textbook does as much and it is well known in the art what the canonical structure of an antibody is. In addition, Cabilly teaches mixing of antibody chains and segments whereas Applicant teaches binding the antibody to Protein A. The Examiner also contends that Cabilly teaches altered immunoglobulins with the ability to bind two antigens simultaneously, ease of preparation and high sensitivity (see Advisory Action at

page 4, lines 8-11). Applicant responds that these are standard properties of antibodies while ease of preparation is not part of the claims.

The Examiner notes that other embodiments of Cabilly were relied on in rejecting the claims but does not state what they are. In the Advisory Action (page 3, lines 4-10), the Examiner contends that Applicants are themselves vague in requesting additional detail on this matter since the references were supplied and Applicants have not specified what additional embodiments are being referred to. Applicants reiterate that it is the Examiner than has referred to "additional embodiments" and the Applicants are simply asking what they are since there is no way to respond to them otherwise.

Because Dorval teaches antibodies useful in *in vitro* assays whereas Cabilly's chimerics are intended for *in vivo* administration, the Examiner tries to show that Cabilly et al also disclose an *in vitro* ELISA assay. However, the ELISA (Figure 10) in Cabilly (described at column 26, lines 4 to 24) is a sandwich assay designed to demonstrate that the resulting antibody is actually chimeric in nature by showing that it has the antigen-binding specificity of the chains from one species and the heavy chain antigenicity of the antibody of a different species. Such an assay has nothing to do with the suggested uses of the chimeric antibody and thus there is no suggestion to use such chimeric antibodies for any *in vitro* purposes at al. The only suggested uses in Cabilly are for preventing immune responses in the recipient animal.

In sum, there is no motivation to combine Dorval et al. and Cabilly et al. and, in fact, doing so would not achieve Applicant's invention because Applicant blocks the Fc site with Protein A whereas Cabilly relies on matching the heavy chain to the recipient animal with no Fc blocking.

2. Applicant's claims 1 and 8-10 were rejected under 35 U.S.C. 103(a) as unpatentable over Sano (U.S. Pat. No. 5,665,539) in view of Cabilly et al (U.S. Pat. No. 4,816,567).

Sano et al (U.S. Pat. No. 5,665,539) ostensibly teaches an immunoglobulin having an antibody portion and a Streptavidin-Protein A portion.

Applicant contends that there is no reason to combine Sano et al with Cabilly et al. Sano teaches a means of detecting an antigen by binding an antibody to it wherein the antibody is attached to a DNA that can be amplified (i.e., detected) using the polymerase chain reaction and Protein A is taught as part of a complex to attach the DNA to the antibody.

The unique feature of Cabilly is having light and heavy chain regions from different species to avoid unwanted binding at the Fc site (located on the heavy chain). Sano discloses a method for detecting antibody binding to an antigen via PCR of a DNA attached to the heavy chain (through Protein A, which binds the Fc site). Again, there is no motivation to use Cabilly's recombinant chimeric antibodies (with an Fc portion from a different species than the portion that binds antigen) if you are just going to tie up that Fc portion with a Protein A complex that binds DNA.

In sum, all one needs to do the assay taught by Dorval or by Sano is an antibody specific for the antigen to be detected and that will complex with Protein A (on the Fc portion – common to all antibody heavy chains regardless of what species they are from) and not the recombinant chimerics taught by Cabilly for a very special use.

No additional fee is believed due in filing this brief. The Commissioner is authorized to charge payment of any additional filing fees associated with this communication or credit any overpayment to Deposit Account No. 03-0678.

EXPRESS MAIL CERTIFICATE

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Deposit Date: 27 August 2004

I hereby certify that this paper and the attachments hereto are being deposited today with the U.S. Postal Service "Express Mail Post Office To Addressee" service under 37 CFR 1.10 on the date indicated above addressed to:

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Alan J. Grant 8/27/04
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Respectfully submitted,

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APPENDIX

APPEALED CLAIMS

1. A blocked immunoglobulin comprising an antibody portion and a Protein A portion wherein said antibody portion comprises a member selected from the group consisting of two antibody light chain variable regions, two antibody heavy chain variable regions and a combination thereof.

2. The blocked immunoglobulin of claim 1 wherein said antibody portion comprises at least one antibody light chain variable region.

3. The blocked immunoglobulin of claim 1 wherein said antibody portion comprises at least one antibody heavy chain variable region.

4. The blocked immunoglobulin of claim 1 wherein said antibody portion comprises at least one antibody light chain variable region and at least one antibody heavy chain variable region.

8. The blocked immunoglobulin of claim 1 wherein said antibody portion comprises at least one antigen-reactive fragment.

9. The blocked immunoglobulin of claim 1 wherein said Protein A portion comprises at least one protein A compound.

10. The blocked immunoglobulin of claim 9 wherein said Protein A compound is a fragment of Protein A.

11. The blocked immunoglobulin of claim 1 further comprising a solid support to which said immunoglobulin is attached.

12. The blocked immunoglobulin of claim 11 wherein said immunoglobulin is attached to said solid support through a covalent linkage.

13. The blocked immunoglobulin of claim 11 wherein the antibody portion of said immunoglobulin is attached to said solid support.

14. The blocked immunoglobulin of claim 11 wherein the antibody portion of said immunoglobulin is attached to said solid support through a tether.

15. The blocked immunoglobulin of claim 11 wherein the Protein A portion of said immunoglobulin is attached to said solid support.

16. The blocked immunoglobulin of claim 11 wherein the Protein A portion of said immunoglobulin is attached to said solid support through a tether.

17. The blocked immunoglobulin of claim 11 wherein the solid support is made of

a material selected from the group consisting of acrylamide, agarose, cellulose, nitrocellulose, glass, polystyrene, polyethylene vinyl acetate, polypropylene, polymethacrylate, polyethylene, polyethylene oxide, polysilicates, polycarbonates, teflon, fluorocarbons, nylon, silicon rubber, polyanhydrides, polyglycolic acid, polylactic acid, polyorthoesters, polypropylfumerate, collagen, glycosaminoglycans, and polyamino acids.

18. The blocked immunoglobulin of claim 11 wherein the solid support further comprises a member selected from the group consisting of thin film, membrane, bottles, dishes, fibers, woven fibers, shaped polymers, particles, beads, microparticles, and a combination of the foregoing.